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Progesterone, progestins and psychosomatic health of women

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Abstract

Psychosomatics as a medical perspective and discipline focuses on the interaction of physical and mental health in the specific life situation of a patient, taking into account the physical and emotional well-being, role functioning, satisfaction with the partner and family relationship, as well as sexual function and satisfaction. There are two important effects of progesterone on the combined physical, mental and sexual well-being of the climacteric patient. The first is the antiestrogenic effect of progesterone on the peripheral physical level which not only protects the endometrium against overstimulation but also reduces individual suffering from heavy bleeding, breast tension, bloating and general discomfort. The second effect is due to the complex action of progesterone in the brain. Studies using different progestins in different dosages and in different regimens show contradictory results. Some studies demonstrate an increase in depressed mood and reduced well-being while using synthetic progestins. Other studies, however, indicate an anxiolytic and sometimes antidepressant effect of progesterone and progesterone-like progestins with an improvement of emotional well-being and quality of life. In the individual patient, the positive or negative emotional and mental state can be conditioned by various pathways of progesterone and progestins. The antiestrogenic effect can attenuate the psychotropic effect of estradiol (E2) on the brain, thus reducing emotional well-being. Progesterone interacting with many brain areas can have a mood stabilizing and anxiolytic effect through the action on the GABA receptor. This effect seems to be strongest when using natural progesterone and the effect varies considerably among different progestins and different dosages due to metabolic pathways involving the production of allopregnanolone or other metabolites. In conclusion, the positive anxiolytic and sedative effects of progesterone on the central nervous system depend on the type of progestogen, the dosage, the timing of application, the combination with estrogen, etc. Progesterone and progestins have important potential to maintain or improve the psychosomatic health of women. Their use must, however, be tailored to specific symptom clusters and to the individual's pre-existing psychosomatic health status.

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Introduction

Psychosomatics as a medical perspective and discipline focuses on the interaction of physical and mental health in a specific life situation of a patient, taking into account the physical and emotional well-being, role functioning, satisfaction with the partner and family relationship, as well as sexual function and satisfaction. It is therefore close to the concept of quality of life but it is less focused on separate aspects but more on the interaction between the different health parameters (1).

We attempted to evaluate the importance of progesterone and progestins on different components of the quality of life of women including somatic and mental health as well as well-being and role functioning.

Progesterone has many functions in the female body, including: as a precursor of estrogen and testosterone, it gives protection to the endometrium, its reproductive capacity, its neuronal integrity, it is a natural diuretic, it helps use fat for energy, helps thyroid hormone action, helps normalize blood sugar levels, normalizes zinc and copper levels, and restores proper cell oxygen levels.

These actions contribute to the positive role of progesterone in reproductive health, bone health, cardiovascular health and neurological health. Apart from these protective and health-maintaining effects, progesterone alleviates estrogen-induced symptoms such as heavy bleeding, breast tension, nervousness, sleep disturbances, etc.

The action of progesterone on the brain, however, is manifold and complicated, which is indicated by the large number of brain regions that have progesterone receptors and by the fact that progesterone exerts genomic and non-genomic actions (2).

In clinical practice, we have to distinguish between the use of natural progesterone and synthetic progestins. Both have typical clinical indications which they share, such as in endometriosis, disorders of the endometrium and endometrium protection. Natural progesterone finds its use in assisted reproductive techniques (ART) and prevention of threatened abortion and could have future use in cardiovascular prevention.

Synthetic progestins are used in contraception. In combined hormonal contraceptives, they have a protective effect on the endometrium and ovarian cancer. Synthetic progestins have known risks regarding cardiovascular disease and breast cancer. These risks depend, however, on the molecular struc-

ture of the progestin and whether they are used in combination with synthetic estrogens (3).

Is progesterone good or bad for the global well-being of the woman?

The results of clinical studies are controversial and show the complexity of the progesterone action. Some studies point to a more negative effect of progestins on mental well-being and mood.

Hammarbäck et al. (4) studied the effect of exogenously administered sequential estrogen/progestin postmenopausal replacement therapy on mood and physical signs. They included 22 women requiring postmenopausal estrogen and divided the women into two groups. The first group of 11 women were given estradiol treatment only (oestrogel cream, 3 mg percutaneously/day) for 21 days with a subsequent break of 7 days. The other 11 women were given in addition a synthetic progestin (lynestrenol, 5 mg/day) during the last 11 days of treatment.

The group with estrogen treatment only did not show any cyclical worsening in mood or physical signs during the treatment. The women who in the latter stage of the estrogen treatment cycle also received progestogen showed significant cyclicity in both moods and physical signs, with a maximum symptom degree during the final days of gestagen treatment. The negative mood change started 1–3 days after progestogen was added to the treatment. The authors concluded that these results suggest that progestins are involved in causing cyclical symptom changes seen in the premenstrual syndrome (PMS).

In a further publication, Bäckström et al. (5) concluded that in ''hysterectomized women only estrogen replacement is strictly necessary. Indeed, there is no imperious need for administrating progesterone/synthetic progestins other than for preventing the risk of endometrial hyperplasia and/or cancer''. Characteristically, hysterectomized women show better and longer compliance to treatment than women without hysterectomy. This should be taken as a strong indicator that it is the side effects generated by progestins which together with bleeding hamper long-term hormone replacement therapy compliance.

Magos et al. (6) investigated possible negative effects of progestogens on mood. This was a prospective placebo-controlled study investigating the influence of norethisterone on mood and behavior. A total of 58 postmenopausal hysterectomized women were treated with subcutaneous estradiol and testosterone implants. Norethisterone, 2.5 or 5 mg daily, was given for 7 days and a placebo for two periods of 7 days. There were widespread adverse effects which were dose-related. Significant changes in five of the eight symptom complexes studied (pain, concentration, behavioral change, water retention and negative affect) were found with 5 mg/day of norethisterone acetate. The symptoms were similar to the typical complaints of PMS, such that a combination of estradiol and testosterone implants with cyclical oral norethisterone appeared to be a model for this condition. The authors concluded that the dose of this progestogen should therefore be the minimum to achieve the desired therapeutic effect.

Other studies came to different conclusions showing more positive effects of other progestins on mood such as anxiolytic and even antidepressant action. Siddle et al. (7) studied 16 postmenopausal women who received conjugated equine estrogens, 1.25 mg/day, continuously. They were randomly allocated to add dydrogesterone, 20 mg/day, for 12 days each calendar month for 3 months and then 10 mg/day in an identical manner for a further 3 months, or to receive the dydrogesterone doses in reverse sequence. Anxiety and physical and psychological status were significantly improved after 3 months of therapy. Significant benefits on depression were less clearly observed. There were no differences between the two dydrogesterone doses on anxiety, depression and physical and psychological status and, overall, the addition of the progestogen did not antagonize estrogen benefits.

Cagnacci et al. (8) published a randomized, placebo-controlled study of 120 postmenopausal women on continuous hormone replacement therapy with transdermal estradiol (50 μg/day) who were receiving for 10 out of every 28 days four different progestins: dydrogesterone (DYD; 10 mg/day; $n=20$), medroxyprogesterone acetate (MPA; 10 mg/day; $n=20$), nomegestrol acetate (NMG; 5 mg/day; $n=20$), or norethisterone acetate (NETA; 10 mg/day; $n=20$).

Anxiety, by the state-trait anxiety inventory, and depression, by the self-evaluation depression scale of Zung, were evaluated just prior to and in the last 2 days of the 10-day progestins adjunct.

Anxiety was decreased by DYD ($-2.3+1.1$; $p<0.01$) and MPA ($-1.5+0.5$; $p<0.01$), but not by NMG or NETA. Depression did not significantly increase during progestins and actually decreased during MPA ($-3.0+0.7$; $p<0.01$). Only the effect of DYD on anxiety and that of MPA on depression were significant compared to the control group ($p<0.05$).

From these studies, it became clear that effects on well-being and mood are not only dose-dependent but also depend on the type of progestin used. Progestins with a structure very close to natural progesterone seem to have a desirable anxiolytic and sedative effect, whereas synthetic progestins derived from androgens can lead to depressive mood states, possibly through their pronounced antiestrogenic action.

Other studies indicate that the effect also depends on pre-existing clinical conditions of the women using progestogens.

Andreen et al. (9) investigated the effect on mood and physical symptoms of two dosages of natural progesterone and a placebo in postmenopausal women with and without a history of PMS.

They included 36 postmenopausal women with climacteric symptoms. The women received 2 mg estradiol continuously during three 28-day cycles. Vaginal progesterone suppositories of 800 mg/day, 400 mg/day, or placebo were added sequentially for 14 days per cycle. The following results were found. Women without a history of PMS showed cyclicity in both negative mood and physical symptoms while on

400 mg/day progesterone but not on the higher dose or the placebo. Women without a history of PMS had more physical symptoms on progesterone treatment compared with placebo. Women with prior PMS reported no progesterone-induced symptom cyclicity. The authors concluded that the addition of progesterone in postmenopausal women can have an opposite effect on cyclic physical and emotional symptoms depending on the pre-existing vulnerability of estrogen/progesterone exposition and that there was a dose-related effect.

Another area to study effects of progestogens on mood is in women who take oral contraceptives (OC). Joffe et al. (10) performed a nested case-control study within a community-based cohort of 976 premenopausal women in the US. They showed that of 658 women on OC, 16.3% of the women reported OC pill-related premenstrual mood deterioration, 12.3% of the women reported premenstrual mood improvement. In adjusted models, previous depression was the only significant predictor of mood deterioration [odds ratio (OR) 2.0; 95% confidence interval (CI) 1.1–3.8]; early-onset premenstrual mood disturbance and dysmenorrhea were significant predictors of OC pill-related mood improvement (OR 3.1; 95% CI 1.9–5.2 and OR 2.3; 95% CI 1.4–3.9, respectively).

The authors concluded that OC pills do not influence premenstrual mood in most women. Premenstrual mood is most likely to deteriorate in women with a history of depression and to improve in women with early-onset premenstrual mood disturbance or dysmenorrhea.

Similar results were published by Oinonen and Mazmanian (11). In their meta-analysis, they found that compared with non-users, OC users experience less variability in effect across the entire menstrual cycle and less negative effect during menstruation (i.e., withdrawal bleeding). They examined in women with OC-related negative mood and effect change as to whether there were potential mediators of the relationship between OCs and mood or effect, and they identified the following mediators: history of depression, psychiatric symptoms, dysmenorrhea, and premenstrual mood symptoms prior to OC use; a history of pregnancy-related mood symptoms; a family history of OC-related mood complaints; being in the postpartum period; and age.

Furthermore, a lower ratio of progesterone to estrogen was associated with more negative mood change in women with a history of premenstrual emotional symptoms, higher progesterone to estrogen ratios are associated with increased negative mood effects in women without such a history, and monophasic OCs have a greater stabilizing effect on mood than triphasic OCs.

There seems to be a group of women, especially those with pre-existing PMS, premenstrual dysphoric disorder (PMDD) or affective disorder, who suffer either from the fluctuation of progesterone or/and from the shift of the estrogen/progesterone ratio to an estrogen dominant state. These women benefit from prescription of progesterone or a natural progestogen for their psychosomatic health.

Rapkin et al. (12) studied healthy OC pill-naive women without current or history of affective disorder. These women received 0.020 mg ethinyl estradiol (E2)-combined with 0.1 mg levonorgestrel as OC for 3 months. They measured serum neuroactive steroids allopregnanolone, allotetrahydrodeoxycorticosterone, and dehydroepiandrosterone (DHEA); neuroactive steroid precursors P and pregnenolone; E2. Mood and anxiety were assessed by the Premenstrual Syndrome Daily Ratings Form, Beck Depression Inventory, Spielberger State-Trait Anxiety Inventory, and Profile of Mood States.

The combined OC pill resulted in a decrease in neuroactive steroids and neuroactive steroid precursors as well as in E2. However, this decline was not associated with adverse mood changes on any of the well-validated assessment tools.

Healthy women without underlying mood or anxiety disorder who were given a low-dose OC pill did not experience adverse psychological symptoms despite a significant reduction in neuroactive steroids.

How to explain controversial empirical results?

There are several possible explanations for the complex and sometimes unpredictable action of progesterone or progesterone derivatives in these women (4, 7, 8).

The differential action of progesterone metabolites on the GABA receptor

GABA receptor activation through chloride channels opening is induced by allopregnanolone, epipregnanolone, androstenedione and androsterone, thus producing a sedative and anxiolytic effect. Other metabolites such as dehydroepiandrosteronesulfate (DHEAS), pregnenolone, pregnenolone sulfate and corticosterone have an opposite chloride channel closing effect on the GABA receptor, thus producing an arousal state. Clinical examples of symptoms and disorders caused by the differential action of GABA steroids are sedation, memory and learning disturbance, clumsiness, increased appetite, worsening of petit mal epilepsy, negative mood such as tension, irritability and depression during hormone treatment, and PMDD. A malfunctioning GABA-A receptor system or genetically determined metabolic pathways leading to a disbalance of metabolites can thus be related to stress sensitivity, concentration difficulties, loss of impulse control, irritability, anxiety and depression. A well-functioning GABA system and well-balanced metabolism, by contrast, can exert positive mood stabilizing, anxiolytic and sedative actions.

The effect of dosage

Animal and human studies show that GABA-A receptor-positive modulators such as barbiturates, benzodiazepines, alcohol and allopregnanolone have a bimodal effect. In pharmacological concentrations, they are central nervous system depressants, anesthetic, antiepileptic and anxiolytic. In low dosages and concentrations, reached endogenously, they can induce adverse emotional reactions in up to 20% of individuals.

The effect of GABA steroids

GABA steroids can also induce tolerance to themselves and similar substances, and rebound occurs at withdrawal. A continuous exposure to GABA steroids causes tolerance, and women with PMDD are less sensitive to GABA-A modulators. An example of withdrawal effect is ''catamenial epilepsy'', when seizures increase during menstruation after the withdrawal of GABA steroids.

There is a direct link between stress and GABA steroids. The adrenals produce specific GABA steroids under stress and this production is individually different. The variable antiestrogenic effect of various progestins can lead to depressive symptoms and diminution of emotional well-being (13, 14).

Consequences and conclusions from a psychosomatic perspective

Progesterone plays a very basic multifunctional role in the female body including the brain, with effects modulated by time of exposure, dosage, metabolism, tolerance, withdrawal, etc. The common denominator of the action is balancing and stabilizing the endocrine, physical and emotional milieu. Progesterone is linked to the stress reaction and is thus part of the stress response system. At present, the clinical task consists of enhancing the balancing, stabilizing and protective actions of progesterone and progestogens by individualizing treatment:

- Look for physical and emotional symptoms indicative of progesterone deficiency.
- Choose a progestogen as natural as possible with an individualized dosage.
- Continuously adapt the dosage according to the symptoms.
- If necessary (in the case of complex symptomatology and insufficient response) integrate treatment into a disorder specific therapy including cognitive behavioral therapy and eventually psychopharmacological treatment.

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